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Genetic Disposition to Inflammation and Response to Antidepressants in Major Depressive Disorder

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Abstract

Background: Inflammation may play an important role in depression and its treatment. A previous study found that increased C-reactive protein (CRP), a marker of systemic inflammation, is associated with worse response to the serotonergic antidepressant escitalopram and better response to the noradrenergic antidepressant nortriptyline. It is unclear whether this reflects genetic disposition to inflammation.

Methods: We analyzed genotype data and weekly Montgomery-Åsberg Depression Rating Scale scores (MADRS) from 755 unrelated individuals obtained over a 12-week period in the Genome-Based Therapeutic Drugs for Depression (GENDEP) study. We calculated a polygenic risk score for CRP level based on genome-wide meta-analysis results from the CHARGE Consortium.

Results: A higher polygenic risk score for CRP was associated with slightly better response to escitalopram and slightly worse response to nortriptyline, reflected in a statistically significant interaction between polygenic risk score and drug ($\beta = 1.07$, 95% CI = 0.26-1.87, $p = 0.0093$).

Discussion: A differential association between CRP-PRS and antidepressant drug that is in a direction opposite to that found with serum CRP measurement suggests that previously observed effect of inflammation on antidepressant efficacy may be driven by state factors distinct from genetic influences on systemic inflammation.

Keywords: Major depressive disorder, antidepressant efficacy, inflammation, C-reactive protein, polygenic risk score

Major depressive disorder (MDD) is a common psychiatric illness associated with substantial personal and socioeconomic burden. It affects more than 350 million individuals worldwide and it is a leading cause of disability (WHO, 2012). MDD is typically treated with antidepressants. However, less than 50% of individuals diagnosed with depression achieve satisfactory improvement following treatment with their first antidepressant (Trivedi et al., 2006). The current trial-and-error approach to treating depression is difficult for patients and often delays recovery (Steimer et al., 2001). Even after multiple attempts at pharmacological treatment of depression, approximately one third of individuals do not respond to conventional antidepressants (Rush et al., 2006). Therefore, there is a pressing need to identify reliable predictors to indicate which individuals will likely respond better to one antidepressant over another.

The immune system, and specifically the inflammatory response, has been implicated in depression and its pharmacological treatment. Psychosocial stress elicits an immune response, resulting in inflammation (Bierhaus et al., 2003). Elevated inflammation following an exposure to a stressor increases the likelihood of developing depression (Aschbacher et al., 2012). Increased serum concentration of an inflammatory biomarker has also been shown to predict more severe symptoms among those with MDD (Köhler-Forsberg et al., 2017). Additionally, individuals who have experienced early life stressors that are associated with later development of depression, such as childhood maltreatment, show increased inflammatory responses to lab stressors and increased levels of inflammation in adulthood (Baumeister et al., 2016; Nanni et al., 2012; Pace et al., 2006). Importantly, higher levels of systemic inflammation may also be associated with inadequate response to pharmacological treatments (Strawbridge et al., 2015).

C reactive protein (CRP) is a reliable marker of systemic inflammation and it is readily testable in most medical laboratories (Miller et al., 2009). It has been demonstrated that CRP level can differentially predict who will respond better to two antidepressants with distinct mechanisms of action. Individuals with low baseline CRP levels ($<1\text{mg/L}$) have been shown to respond better to the serotonergic antidepressant escitalopram and individuals with higher baseline CRP respond better to the noradrenergic antidepressant nortriptyline (Uher et al., 2014). CRP and its interaction with drug explained more than 10% of the individual-level variance in treatment outcome (Uher et al., 2014). This finding has been partially replicated in an independent sample of MDD patients, where individuals with high serum CRP ($>1\text{mg/L}$) showed lower rates of remission with escitalopram monotherapy than those with lower serum CRP levels (Jha et al., 2017). However, single measurements of CRP can be easily perturbed by state factors such as recent infections, injuries, body mass index (BMI), or inflammatory conditions (Kathiresan et al., 2006). Additionally, the effects of some genetic variants on levels of CRP may be conditional on BMI (Dehghan et al., 2011). It is therefore desirable to examine more stable indicators of propensity to systemic inflammation.

Genetic factors likely influence both serum CRP levels and response to antidepressants (Tansey et al., 2013). It has been shown that serum CRP is approximately 50% heritable and specific genetic variants associated with serum CRP have been identified (Dehghan et al., 2011; Sas et al., 2017). Polygenic risk scores (PRS) allow us to test the aggregate effects of hundreds to thousands of variants across the genome on a given phenotype. Using this methodology, it is possible to index an individual's genetic liability to systemic inflammation. The aim of the present study was to test if a polygenic risk score for CRP predicts response to escitalopram and nortriptyline in the same direction as serum CRP levels. We calculated polygenic risk score

(CRP-PRS) for escitalopram- and nortriptyline-treated individuals based on the CHARGE consortium genome-wide meta-analysis of CRP levels (Dehghan et al., 2011). Participants who were treated with either drug with both weekly depression symptom ratings and genotype data were drawn from the Genome-based Therapeutic Drugs for Depression (GENDEP) study (Uher et al., 2010). We hypothesized that individuals with a lower CRP-PRS would show better response to escitalopram and that individuals with a higher CRP-PRS would show better response to nortriptyline.

Methods

1. Target Sample

1.1 Sample description

The target sample was composed of 755 unrelated individuals from the Genome-based Therapeutic Drugs for Depression (GENDEP) project with genome-wide SNP data and Montgomery-Åsberg Rating Scale for Depression (MADRS) scores. Participant characteristics are shown in Table 1. The GENDEP project is a multi-center partially randomized clinical and pharmacogenetic study including 811 treatment-seeking individuals diagnosed with unipolar depression of at least moderate severity according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) or ICD-10 (International Classification of Diseases, 10th revision) criteria, established using the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) semi-structured interview. Participants ranged in age from 19-72 years and were of Caucasian European ancestry. Exclusion criteria were a family history of bipolar disorder in first-degree relatives, lifetime personal history of schizophrenia or bipolar disorder, current substance dependence, and pregnancy (Uher et al., 2010). Participants were allocated to receive

treatment with one of two antidepressant drugs: nortriptyline (50-150 mg daily) or escitalopram (10-30 mg daily). Participants with no contraindications were randomly allocated to receive either nortriptyline or escitalopram. Participants with contraindications for one antidepressant were non-randomly allocated to the other drug. The present study includes 432 participants treated with escitalopram and 323 participants treated with nortriptyline with both genotype data and weekly MADRS scores. The GENDEP project was approved by ethics boards of participating centers, and all participants provided written informed consent.

1.2 Antidepressant Response

The outcome measure of the present study was total score on the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979), administered weekly for 12 weeks by trained psychiatrists and psychologists with high interrater reliability (Uher et al., 2012, 2008).

1.3 Genotyping, Quality Control, and Imputation

We genotyped 550,337 single nucleotide polymorphisms (SNPs) with Illumina Human610-quad chip in DNA extracted from peripheral blood samples obtained at baseline (Uher et al., 2010). Additional genotyping was performed using the Illumina Infinium Exome-24 v1.0 BeadChip that includes ~ 250K coding variants. We completed pre-imputation quality control on genome-wide and exome array data by excluding variants and participants according to the following criteria: 1) variants with missing rate $\geq 5\%$; 2) monomorphic variants; 3) participants with genotyping rate $< 97\%$; 4) participants with sex discrepancies between self-reported sex and genetic sex; 5) participants with abnormal heterozygosity; 6) related participants (identity by descent (IBD) > 0.1875) (Anderson et al., 2010); 7) population outliers according to Eigensoft analysis of linkage-disequilibrium-pruned genetic data (Patterson et al.,

2006; Price et al., 2006); and 8) GWAS discordant participants (for exome data only). Hardy–Weinberg equilibrium was tested, but was not used as an exclusion criterion for markers because departures from Hardy–Weinberg equilibrium are expected in a case-only study (Wittke-Thompson et al., 2005).

Data were imputed using Minimac3 via the Michigan Imputation Server (<https://imputationserver.sph.umich.edu/start.html>). Post-imputation quality control consisted of pruning variants with poor imputation quality (R^2 score < 0.30) (Li et al., 2010; Pistis et al., 2015) or minor allele frequency (MAF) < 0.01.

2. Polygenic Risk Scores

2.1 Reference Sample for Polygenic Risk Score Derivation

We constructed the CRP-PRS based on the results from the CHARGE Consortium meta-analysis of genome-wide association data for CRP levels (Dehghan et al., 2011). It has been demonstrated that a genetic risk score based on these results predicts plasma CRP in a reproducible fashion, explaining approximately 5% of the variance in CRP levels (Dehghan et al., 2011).

2.2 Polygenic Risk Score Calculation

We constructed the CRP-PRS using PRSice (Euesden et al., 2015). We pruned genotypes using clumping to obtain an independent set of SNPs in linkage equilibrium with an $r^2 < 0.1$ within any 250kb window. In the context of phenotypes with polygenic inheritance, it has been shown that the predictive value of polygenic risk scores is improved with the inclusion of more weakly associated variants that do not meet the threshold for genome-wide significance (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Wray et al., 2018). Therefore, we constructed four CRP-PRS according to SNP associations with CRP levels, with p-value (P_T)

thresholds of 0.05, 0.1, 0.2, and 0.4, weighting the contribution of each associated allele by the effect size of its association with CRP levels in the CHARGE meta-analysis.

3. Testing the effects of CRP-PRS on antidepressant drug response

We examined the association between each CRP-PRS and change in MADRS score from baseline to week 12 among escitalopram- and nortriptyline-treated individuals in mixed-effects models for repeated measurements (MMRM) with baseline depression severity (MADRS), age, sex, recruitment centre, two ancestry informative dimensions generated using multidimensional scaling analysis, linear and quadratic effects of time in treatment as fixed covariates. Non-independence of repeated measurements from the same participant was accounted for by a random effect. We implemented the MMRM in STATA-15, as previously described (Uher et al., 2014). We tested our primary hypothesis as an interaction between drug (escitalopram vs. nortriptyline) and CRP-PRS in MMRM. To correct for multiple tests of the same hypothesis with four CRP-PRS p-value thresholds, we set the significance threshold at a False Discovery Rate Q-value < 0.05 .

4. Sensitivity Analysis

To examine the influence of body mass index (BMI) on our results, we conducted sensitivity analysis by including BMI as a covariate in the model described above. We examined the association between the CRP-PRS with the p-value (P_T) threshold of 0.2 and change in MADRS score from baseline to week 12 among escitalopram- and nortriptyline-treated individuals in mixed-effects models for repeated measurements (MMRM) with baseline depression severity (MADRS), age, sex, recruitment centre, two ancestry informative dimensions generated using multidimensional scaling analysis, linear and quadratic effects of time in treatment, and baseline

BMI as fixed covariates. Non-independence of repeated measurements from the same participant was accounted for by a random effect.

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Results

Predicting response to escitalopram

Among the 432 escitalopram-treated participants, the CRP-PRS with $P_T = 0.2$ was nominally significantly associated with better therapeutic response (beta = -0.58, 95% CI = -1.10, -0.06, $p = 0.028$), but the association did not remain significant after correction for multiple testing across the four CRP-PRS with varying P_T ($q = 0.11$). While the CRP-PRS with $P_T = 0.2$ showed a relatively stronger trend for prediction, the direction of association was consistent across the four CRP-PRS, with higher CRP-PRS scores being associated with slightly better response to the serotonin-reuptake inhibiting antidepressant escitalopram (see Figure 1).

Predicting response to nortriptyline

Among the 323 nortriptyline-treated participants, the CRP-PRS were not significantly associated with therapeutic response. Of the four CRP-PRS, the one with $P_T = 0.2$ showed a relatively stronger trend for prediction (beta = 0.51, 95% CI = -0.10, 1.12, $p = 0.10$, $q = 0.41$). The direction of the non-significant association was consistent across the four P_T , with lower CRP-PRS scores being associated with slightly better response to the norepinephrine-reuptake inhibiting antidepressant (see Figure 1).

Interaction between polygenic risk score and antidepressant drug

We found a statistically significant interaction between CRP-PRS with $P_T = 0.2$ and antidepressant drug (beta = 1.07, 95% CI = 0.26, 1.88, $p = 0.009$), reflecting a better response to escitalopram and worse response to nortriptyline with increasing CRP-PRS score. This

interaction remained statistically significant after correcting for multiple comparisons ($q = 0.04$, see Table 2).

Sensitivity analysis

Accounting for baseline BMI did not appreciably change our findings. The statistically significant interaction between CRP-PRS with $P_T = 0.2$ and antidepressant drug persisted when accounting for BMI (beta = 1.06, 95% CI = 0.25, 1.86, $p = 0.010$), reflecting a better response to escitalopram and worse response to nortriptyline with increasing CRP-PRS score. The full results of the sensitivity analyses can be found in the Supplementary Materials.

Discussion

We tested the value of a polygenic risk score for systemic inflammation (CRP-PRS) in predicting response to the serotonergic antidepressant escitalopram and the noradrenergic antidepressant nortriptyline. We found that individuals with a lower CRP-PRS responded slightly better to nortriptyline and individuals with a higher CRP-PRS responded slightly better to escitalopram. These results were independent of BMI. The direction of the interaction between CRP-PRS and antidepressant drug was opposite to that found using measured serum CRP.

The present investigation was motivated by the need to identify a mechanism underlying a potentially meaningful association between systemic inflammation and antidepressant treatment response in depression. We previously found that individuals with higher serum CRP respond better to nortriptyline and worse to escitalopram (Uher et al., 2014). We hypothesized that this differential response could be driven by a genetic disposition to systemic inflammation. However, when we replaced measured serum CRP with a polygenic score indexing genetic liability to systemic inflammation (CRP-PRS), the direction of association was reversed. This finding suggests that the genetic factors contributing to CRP levels may be distinct from those

directly influencing antidepressant response. This result is consistent with a Mendelian randomization study that found no causal effect of CRP level on MDD, despite the known association between depression and inflammation (Prins et al., 2016). Based on both previous research and the results of the present study, it is possible that genetic factors and inflammation independently influence response to antidepressants.

While the absence of association in the expected direction may be consistent with some recent research (Prins et al., 2016), the finding of a significant drug-PRS interaction in the opposite direction to serum CRP is new and surprising. We could speculate that the permanent effect of genetic factors on systemic inflammation may lead to compensatory processes that act in a way opposite to state-dependent changes in systemic inflammation. However, at this point, this remains an interesting result that requires replication before any major conclusions are drawn. Future research could be directed towards examining the joint effects of inflammation and genetics in determining who will respond better to a given antidepressant. If serum CRP measurement is used for treatment selection, it may be important to obtain a recent measurement of CRP as it is likely that a state contributor to systemic inflammation other than a stable genetic effect is responsible for some of the replicated prediction.

The present study benefits from a comparative clinical trial design and thorough assessments of participants across multiple follow-ups. However, our results should be interpreted in the context of its limitations stemming from the combination of the relatively weakly predictive value of the CRP-PRS and a relatively modest sample size. The CRP-PRS used in the present study explains approximately 5% of variance in serum CRP levels (Dehghan et al., 2011). The effect size of the PRS on antidepressant response was unknown prior to the present study. The sample size of 755 individuals allows detecting an effect explaining 0.8% of

variance or more with an adequate power ($>80\%$). This means that we can only expect to detect moderately strong, but not weak effects.

In conclusion, the present findings suggest that the previously observed effect of inflammation on antidepressant efficacy may be due to state factors distinct from genetic influences on systemic inflammation. Genetic and state-dependent influences on systemic inflammation should be considered separately when predicting response to antidepressant drugs.

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Table 1. Participant characteristics.

	Treatment Arm	
	Escitalopram <i>n</i> = 432	Nortriptyline <i>n</i> = 323
Randomized, <i>n</i> (%)	226 (52.3)	222 (68.7)
Female, <i>n</i> (%)	269 (62.3)	203 (62.9)
Age in years, mean (SD)	42.2 (11.5)	42.2 (11.6)
Baseline MADRS, mean (SD)	28.5 (6.6)	29.4 (6.8)
MADRS change, % (SD)	54.7 (32.1)	49.3 (32.8)

MADRS change = change in MADRS score from baseline to week 12.

Figure 1. Effects of polygenic risk scores on antidepressant response by drug. Boxes represent the strength of the CRP-PRS at each P_T for each antidepressant-treated group based on the MADRS points change per one standard deviation increase of the PRS. Whiskers represent the 95% confidence interval. Here we also present the uncorrected p-value and the False Discovery Rate (FDR) q-value for the association of each CRP-PRS with response to either escitalopram or nortriptyline.

Drug	CRP-PRS	p-val	q-val
Escitalopram	0.05	0.14	0.14
	0.1	0.12	0.14
	0.2	0.03	0.11
	0.4	0.10	0.14
Nortriptyline	0.05	0.46	0.61
	0.1	0.25	0.50
	0.2	0.10	0.41
	0.4	0.62	0.62

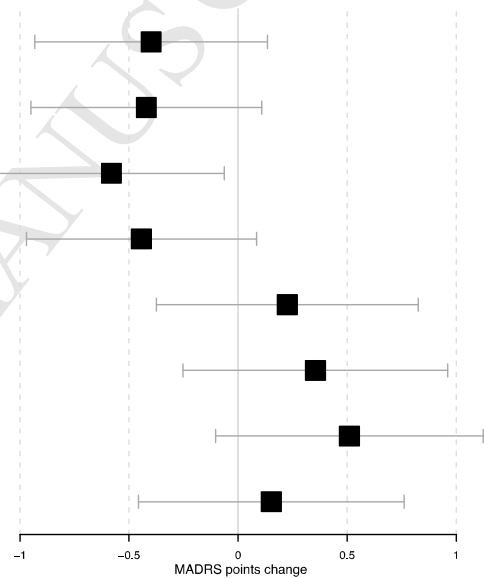


Table 2. Interactions between CRP polygenic risk scores and drug. The P_T values represent the p-value cut-offs. Genetic variants with a p-value of association with serum CRP levels (Dehghan et al., 2011) that falls below each P_T cut-off were retained to create each CRP-PRS. Beta (β) is the interaction regression coefficient indicating the differential change in points of the MADRS score by drug per one standard deviation of CRP-PRS at each P_T . For each CRP-PRS, we used age, sex, baseline depression severity (MADRS), time in study (linear and quadratic), recruitment center, and two ancestry informative dimensions as covariates and $N = 755$. The full results of all regression analyses are in the Supplementary Materials.

CRP-PRS	Number of variants included	β	95% CI	p-value	q-value
$P_T = 0.05$	431	0.55	-0.25, 1.35	0.179	0.179
$P_T = 0.1$	791	0.72	-0.08, 1.53	0.079	0.158
$P_T = 0.2$	1441	1.07	0.26, 1.88	0.009	0.037
$P_T = 0.4$	2661	0.57	-0.24, 1.38	0.169	0.179

Author Contributions

Zwicker was responsible for genetic analyses and drafted the initial manuscript. Fabbri performed quality control and imputation of the GENDEP dataset and reviewed and revised the manuscript. Lewis contributed to study planning, consulted on analyses, reviewed and revised the manuscript. Rietschel, Hauser, Mors, Maier, Zobel, Farmer, Aitchison, McGuffin were investigators on GENDEP and were involved in the design of the GENDEP study and data collection and contributed revisions to the manuscript. Uher conceived the study, supervised analyses and contributed to writing the manuscript and oversaw analyses. All authors read and approved the final manuscript.